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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,054	02/06/2001	Peter Joseph Cassidy	707.025US1	3789

21186 7590 06/25/2009  
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MINNEAPOLIS, MN 55402

EXAMINER
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GROSS, CHRISTOPHER M

ART UNIT	PAPER NUMBER
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1639

NOTIFICATION DATE	DELIVERY MODE
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06/25/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

request@slwip.com

<b>Office Action Summary</b>	<b>Application No.</b> 09/647,054	<b>Applicant(s)</b> CASSIDY ET AL.	
	<b>Examiner</b> CHRISTOPHER M. GROSS	<b>Art Unit</b> 1639	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 08 May 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 113-144 is/are pending in the application.
- 4a) Of the above claim(s) 114-118, 122, 123, 125, 127-133, 136, 139 and 141-144 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 113, 119-121, 124, 126, 134, 135, 137, 138 and 140 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/21/08; 5/8/09</u>   | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Responsive to communications entered 1/21/2008; 9/23/2008; 10/27/2008; 5/8/2009  
Claims 113-144 are pending. Claims 114-118, 122-123, 125, 127-133, 136, 139, 141-144  
are withdrawn. Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are  
under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in  
37 CFR 1.17(e), was filed in this application after final rejection. Since this application is  
eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR  
1.17(e) has been timely paid, the finality of the previous Office action has been  
withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/21/2008 has  
been entered.

### ***Priority***

This application is a 371 of PCT/AU99/00207 03/24/1999 which claims priority to  
AUSTRALIA patent PP2548 03/24/1998. The acceptance notice from DO/EO mailed  
11/1/2006 is in the file.

### ***Withdrawn Rejection(s)***

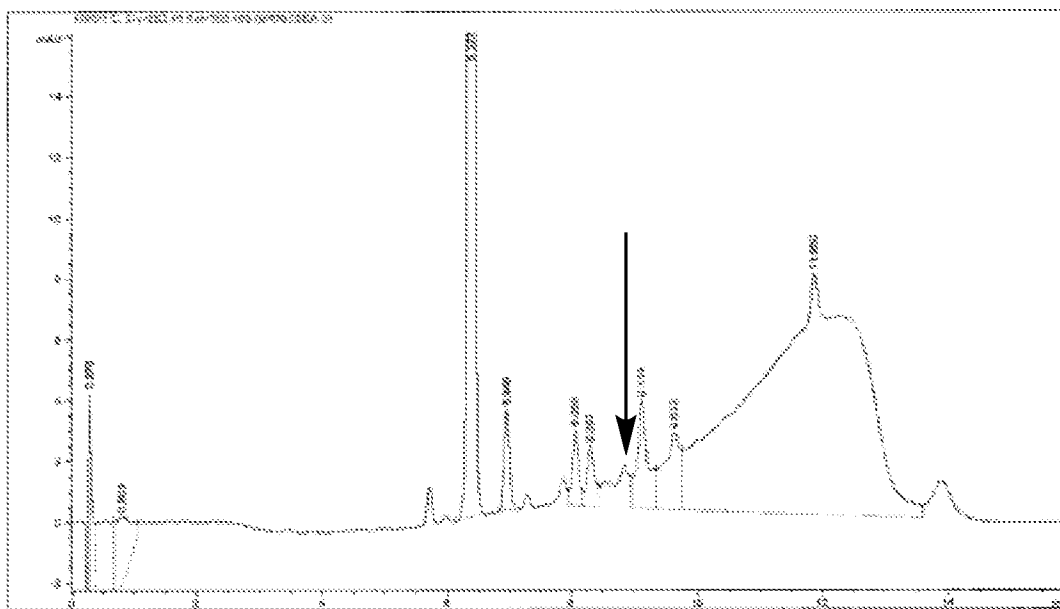
The rejection of claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140  
under 35 U.S.C. 102(b) as being anticipated by Ma et al (1995 Protein Peptide Letters  
2:347-350) is hereby withdrawn in view of applicant's persuasive arguments based  
upon evidence provided in the 1/21/2008 Jenkins and 10/27/2008 Cassidy 37  
CFR 1.132 declarations.

The rejection of claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140  
are rejected under 35 U.S.C. 103(a) as being unpatentable over Gardner et al (1993  
Tetrahedron 49:3433-3448 – IDS entry 9/25/2000) in view of Alkorta et al (1996 J.

Molecular Modeling 2:16-25) is hereby withdrawn in view of applicant's persuasive arguments.

*Response to Declarations*

The declarations under 37 CFR 1.132 filed 1/21/2008 and 10/27/2008 are sufficient to overcome the rejection of claims based upon Ma et al based on the totality of evidence. Nevertheless, by all reasonable interpretation and estimation, a minor peak on p 107 of the 10/27/2008 declaration appears to have a retention time of 8.7 min, the retention time of the 1,4 diazapan-2-one (compound 2) authentic standard prepared by applicant. Said peak, shown below, was not identified in the response to the 37 CFR 1.105 requirement for information mailed 2/4/2009. Applicant is required to indicate the retention time of this peak in response to this office action.



The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ma et al** (1995 Protein Peptide Letters 2:347-350; PTO 892 4/5/2006) in view of **Tsunoda et al** (1996 Tetrahedron Letters 37:2457-2458; PTO 892 1/10/2007) or **Tsunoda et al II** (1993 Tetrahedron Letters 34: 1639-1642) as evidenced by the 1/21/2008 Jenkins declaration.

*Please note, in accordance with MPEP 2121.01 II, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103."* Symbol Techs. Inc. v. Opticon Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991). Here, Ma et al constitutes prior art, despite being argued by applicant as non-enabled with regard to the Mitsunobo reaction (step f in scheme 2).

The claimed invention is drawn to a protein gamma turn mimetic, in which the hydrogen bond is replaced by an ethylene bridge, so as to form a 1,4 diazapan-2-one derivative.

Claims 119, 120, 121, 124, 126,134,135, 137, 138 and 140 represent variations thereof.

**Ma et al** teach throughout the publication and especially the target molecule on p 347, the same 1,4 diazapan-2-one mimetic bearing the tripeptide sequence Ile-Ala/Asp-Gly; therein including R groups being amino acid side chains, Z and Z' being H, M', M'', M3, M4 being H, M5 and M6 are taken together with the carbon atom to which they are attached to from a carbonyl group, RC is the carboxy terminus of the mimetic, PgN is shown as Z (a.k.a. Bzl or Cbz) or Boc in an alternative embodiments in schemes 1 and 2, respectively. Therefore the disclosure of Ma et al reads on claims 113,121,134,135,137 and 138.

Ma et al teach C-terminal protection as an ethyl ester, reading on the protecting group of claim 119 and alkoxy group of claim 120, as well as the protecting group of claim 124,126 and 140.

Evidence provided in 10/27/2008 Cassidy declaration indicates that the final Mitsunobo reaction (f) in scheme 2 of Ma et al provides a N-Boc aziridine (see compound 3 p 7) rather than the desired 1,4 diazapan-2-one mimetic precursor (see compound 2 p 7).

**Tsunoda et al and Tsunoda et al II** teach, throughout the documents and especially the tables in each, tosyl protection of nitrogen rather than Bzl for performing Mitsunobo reactions.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to utilize the tosyl protection of Tsunoda et al or Tsunoda et al II instead of Bzl in step (f) of scheme 2 of Ma et al in preparing the 1,4 diazapan-2-one mimetic.

One of ordinary skill in the art would have been motivated to use utilize the tosyl protection of Tsunoda et al or Tsunoda et al II instead of Bzl in step (f) of scheme 2 of Ma et al 1,4 diazapan-2-one mimetic because Tsunoda et al II state "If HA [protected amine] has a pKa larger than 11, the yield of RA [Mitsunobo product] lowers considerably, and with HA having a larger pKa than 13 the desired reaction does not occur" and BzINH has a pKa considerably greater than 11.

One of ordinary skill in the art would have had a reasonable expectation of success in substituting tosyl per Tsunoda et al or Tsunoda et al II for Bzl protection of nitrogen per Ma et al in preparing the 1,4 diazapan-2-one mimetic because: (i) all three references concern Mitsunobo chemistry, thus the refinements of Tsunoda et al and Tsunoda et al II are well suited toward Ma et al and (ii) even assuming *arguendo* - the Mitsunobo reaction even with Tosyl nitrogen protection does not occur - for what ever reason - according to section 12 of the Jenkins declaration, N-Boc aziridines may nevertheless be opened by acidic sulfonamides (tosyl protected nitrogen) and therein

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provide the desired 1,4 diazapan-2-one mimetic precursor, albeit through an alternative pathway.

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ma et al** (1995 Protein Peptide Letters 2:347-350; PTO 892 4/5/2006) in view of **Tsunoda et al** (1996 Tetrahedron Letters 37:2457-2458; PTO 892 1/10/2007) or **Tsunoda et al II** (1993 Tetrahedron Letters 34: 1639-1642) as evidenced by the 1/21/2008 Jenkins declaration further in view of **Mammi et al** (1985 JACS 107:4008-4013).

**Ma et al in view of Tsunoda et al or Tsunoda et al II is relied on as above.**

Ma et al in view of Tsunoda et al or Tsunoda et al II do not teach a protein gamma turn mimetic with the tripeptide sequence Gly-Phe-Leu.

**Mammi et al** teach, throughout the document and especially table II and figure 7, highly active opioid peptide (enkephalin) analogs bearing the sequence Gly-Phe-Leu (elected species) in a gamma turn conformation stabilized by a hydrogen bond.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to generate an enkaphalin analog of Mammi et al locked into place with an ethylene bridge in the manner of Ma et al in view of Tsunoda et al or Tsunoda et al II.

One of ordinary skill in the art would have been motivated to generate an enkaphalin analog of Mammi et al locked into place with an ethylene bridge in the manner of Ma et al in view of Tsunoda et al or Tsunoda et al II because said hydrogen



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bond is disrupted by water and analogs with additional restraints are desirable, as noted by Mammi et al in the last sentence of the abstract and conclusions section on p 4013.

One of ordinary skill in the art could incorporate Gly-Phe-Leu locked into a gamma turn conformation with an ethylene bridge per Ma et al in view of Tsunoda et al or Tsunoda et al II into the enkephalins of Mammi et al because the Boc protection of Gly (provided by Ma et al) is used in Boc based solid phase peptide synthesis, a robust technique for preparing opioid peptides, such as disclosed by Mammi et al, well recognized in the art.

Therefore, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

### ***New Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

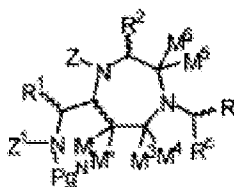
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such

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omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships concern the definitions of  $M^4$ ,  $R^C$ , R and Z. Commensurate with the structure from the claim below:



(a) In section (ii) of claim 113,  $M^4 = M'$ , it is not clear how this is possible and still be a 1,4 diazapan-2-one .

(b)  $R^C$  is selected from the group consisting of  $CH_2R$ , which if R is H, the side chain of the amino acid glycine set forth in the structure it is not clear what structure is chemically possible.

(c) Z is selected from the group consisting of  $CH_2R$  and  $C(O)R$  and suffers similar issues as  $R^C$ .

(d) Further compounding the confusion, the antecedent basis for R is ambiguous. R is set in the structure at a particular location (ca. 4 O' clock) and is also defined as an amino acid side chain. It is not clear if the R in the definition for Z and  $R^C$  refer to the R of the structure or an amino acid side chain.

As currently written, the metes and bounds of the claims are unascertainable. Therefore, claim 113 and all dependent claims are rejected under 35 USC 112, second paragraph.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross  
Examiner  
Art Unit 1639

cg

/ Christopher S. F. Low /  
Supervisory Patent Examiner, Art Unit 1639